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Human alveolar echinococcosis (AE) is a severe hepatic disease caused by *Echinococcus multilocularis*. In France, the definitive and intermediate hosts of *E. multilocularis* (foxes and rodents, respectively) have a broader geographical distribution than that of human AE. In this two-part study, we describe the link between AE incidence in France between 1982 and 2007 and climatic and landscape characteristics. National-level analysis demonstrated a dramatic increase in AE risk in areas with very cold winters and high annual rainfall levels. Notably, 52% (207/401) of cases resided in French communes (smallest French administrative level) with a mountain climate. The mountain climate communes displayed a 133-fold (95% CI: 95–191) increase in AE risk compared with communes in which the majority of the population resides. A case–control study performed in the most affected areas confirmed the link between AE risk and climatic factors. This arm of the study also revealed that populations residing in forest or pasture areas were at high risk of developing AE. We therefore hypothesised that snow-covered ground may facilitate predators to track their prey, thus increasing *E. multilocularis* biomass in foxes. Such climatic and landscape conditions could lead to an increased risk of developing AE among humans residing in nearby areas.

Introduction

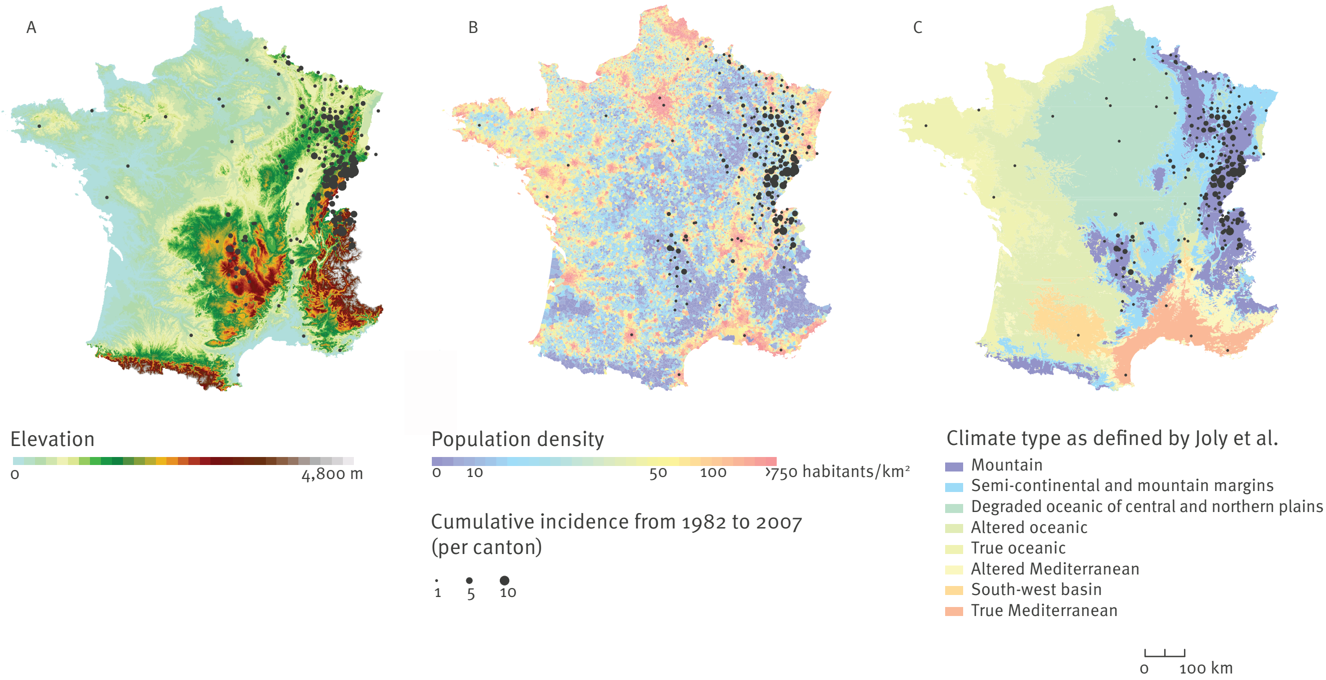
Echinococcus multilocularis is a cestode parasite that exhibits a dixenic life cycle involving circulation between canids and rodents. In France, the *E. multilocularis* sylvatic life cycle involves foxes (the main definitive host) and rodents such as *Arvicola terrestris*, *Microtus arvalis*, *M. agrestis* or *Ondatra zibethicus* (the main intermediate hosts). Humans represent an aberrant host of the parasite, although they sometimes become infected with *E. multilocularis* larvae after ingesting parasite oncospheres. When *E. multilocularis* infects humans, *E. multilocularis* metacestode cells proliferate in the liver and eventually lead to alveolar echinococcosis (AE), a rare but severe hepatic disease resembling a slow-growing liver cancer [1].

A study by the EurEchinoReg network showed that 235 of 559 (42%) European AE cases reported from 1982 to 2000 were observed in France [2]. Since 2000, the French registry of human AE cases has been maintained by the FrancEchino network. In total, 407 human cases were identified from 1982 to 2007 [3]. In France, for this period, high-risk areas included the Massif Central and north-eastern regions of the country (Figure 1), where most cases either resided in rural communes (smallest French administrative level) or resided in towns but worked as farmers or tended gardens [3].

Although behavioural [3-8] and genetic [9-11] elements have been identified as risk factors of human AE, they largely fail to explain the geographical distribution of the disease. For instance, in China, specific landscapes, such as alpine meadows, are associated with an increased prevalence of human AE [8,12]. In Europe and especially in France, an increase in the proportion of grassland is associated with vole density outbreaks.

Figure 1

Location of human alveolar echinococcosis cases with regard to elevation (A), population density (B) and climate type (C), France, 1982–2007 (n = 401)



Panel A illustrates that elevation is not the main factor associated with alveolar echinococcosis (AE) distribution. Panel B shows that cases were not located in densely inhabited areas. Panel C illustrates that AE cases were located in areas with a cold climate.

Joly et al. [21] described the types of climate as follows: Type 1 is characterised by a high number of rainy days, high cumulative precipitation levels, minimal average temperature, maximal number of days with temperatures < −5 °C, minimal number of days with temperatures >30 °C, maximal interannual variability of rainfall in July and maximal interannual variability of temperatures in January and July. Type 2 is a transition from Type 1 to Type 3. Type 2 is characterised by cold January temperatures, slightly lower precipitation levels and less frequent precipitation than Type 1, and a low ratio between autumn and summer rainfall levels. Type 3 is characterised by intermediate temperatures and low precipitation levels, especially during the summer. For Type 3, the interannual variability of rainfall is minimal, while the interannual variability of temperature is high. Other climate types were of little interest regarding AE incidence patterns and were mostly characterised by warmer winter temperatures.

For ethical reasons, case locations are shown at the canton level (fourth French administrative division).

Dietary specialisation has been described in foxes during these outbreaks leading to an increase in the burden of *E. multilocularis* in foxes [13-15]. Nevertheless, human AE case distribution does not correlate with that of grasslands, foxes or rodents. In particular, human AE is very rarely diagnosed in western France, despite the apparent presence of favourable transmission factors regarding landscapes and hosts [13]. Thus, the key environmental and geographical factors associated with human AE transmission remain poorly understood.

In this study, we hypothesised that the completion of the sylvatic life cycle and transmission of the parasite from the animal hosts to humans depend on the climatic and landscape conditions. We first assessed the association between human AE cases and environmental data at a national scale in France. In the French regions with the highest AE incidence rates, we then compared the habitat environment of AE cases with that of randomly selected residences at a local scale.

Methods

This study included all AE cases diagnosed in France from 1982 to 2007. The analyses were performed in two parts. First, at the national level, we assessed AE cumulative incidence in each commune, considering several demographic and environmental variables (e.g. elevation, landscape and climate). France is divided into five nested administrative levels (listed from largest to smallest geographical divisions: régions, départements, arrondissements, cantons and communes). Second, we conducted a case–control study in the nine most affected French départements to compare case habitats (in terms of elevation, landscape and climate) with randomly selected control habitats at various buffer sizes (i.e. circular areas centred over each habitat with a 500 m, 1000 m, 1500 m and 2000 m radius [12,16]).

Data acquisition

Case definition and data collection

Cases were defined as patients with compatible clinical and epidemiological histories and imaging findings or positive specific serology for AE.

Case data were obtained from the FrancEchino network registry, which is supported by the French Institute for Public Health Surveillance (Institut de Veille Sanitaire, InVS). This population-based registry actively collects French AE case data as previously described [17].

Addresses of the cases were registered in a separate anonymous database according to French regulation (Comité National pour l'Informatique et les Libertés and Comité de Protection des Personnes) in the context of biomedical research [18].

We interviewed all pathologists, parasitologists, public university hospital pharmacy staff (who are the only people allowed to deliver albendazole or mebendazole for AE treatment in France) and medicine, radiology and abdominal surgery hospital department staff who treat AE patients.

Environmental data

Demographic data were obtained from the French National Institute of Statistics and Economic Studies (INSEE) [19].

Land cover data were obtained from the European Commission programme to coordinate information on the environment (CORINE) land cover (CLC) 2006 map [20]. Pixel size was 25 m x 25 m. The 44 CLC classes are typically categorised into five groups (agricultural areas, forests and semi-natural areas, artificial surfaces, wetlands, water bodies and open spaces without vegetation). We chose to detail the group 'agricultural areas' into three subgroups (arable and permanent cultures, heterogeneous agricultural areas and pastures) because these types of landscape environments play an important role in the life cycle of foxes and voles, as observed in China and eastern France [12,13,15,16]. We also subdivided the group 'forests and semi-natural areas' into three subgroups (broad-leaf and mixed forest, coniferous forest and shrub and herbaceous vegetation). The group 'artificial surfaces' was left unmodified, while the three remaining groups were recategorised into the class 'other'. For each analysed territory (either commune or buffer around habitats), we calculated the percentage of each CLC class and the mode, i.e. the CLC class covering the largest part of the territory.

Climate data were obtained from Joly et al. [21]. Briefly, the authors provided a set of 15 raster climate maps (with a precision of 250 m x 250 m) that we used to extract 14 variables as follows: annual mean temperature, number of cold days (with minimum temperature less than −5 °C), number of warm days (with maximum temperature above 30 °C), difference in mean temperature between January and July, cumulative annual precipitation, number of rainy days in January, number of rainy days in July, difference in precipitation levels between January and the entire year, difference in precipitation levels between July and the entire year, interannual variability in temperature in January, interannual variability in temperature in July, interannual variability in precipitation in January, interannual variability in precipitation in July, (September + October) precipitation/July precipitation, and an integrative climate typology classifying French climates into eight types (Type 1: mountain; Type 2: semi-continental and mountain margins; Type 3: degraded oceanic of central and northern plains; Type 4: altered oceanic; Type 5: true oceanic; Type 6: altered Mediterranean; Type 7: south-west basin; and Type 8: true Mediterranean) (Figure 1). For each analysed territory (commune or buffer around habitats), we calculated the percentage covered by each variable modality and extracted the mode of each variable.

Elevation data were obtained from the Shuttle Radar Topography Mission (ArcGIS data and maps CD-ROM, Environmental Systems Research Institute (ESRI), Redland, CA, United States) with a precision of 100 m x 100 m.

Selection of control residences

Control residences were selected from the non-professional French telephone directory by applying a computerised algorithm based on a uniform distribution on page, column and line. We randomly selected two addresses from 10,000 inhabitants in each of the nine most affected départements, i.e. the départements with an AE incidence rate greater than the upper limit of the 95% confidence interval (CI) of the mean incidence rate.

Geographical location

Address location at the time of diagnosis was determined using Geoportail [22]. We confirmed the location data using the cadastre registry [23].

When the location of a case (or control) residence could not be accurately determined (e.g. in a hamlet with no street name and no house number), the place of residence was arbitrarily selected as the centre of the corresponding inhabited area. Therefore, the maximum imprecision for case and control residences was less than 500 m.

Cases with insufficient address data were excluded from the buffer analysis.

Statistical analysis

Alveolar echinococcosis distribution in communes at a national scale

Global spatial clustering analysis of AE-affected communes was performed using the Moran's I coefficient.

The relationship between the AE case number of each French commune and each covariable was subjected to univariate analysis using a general linear model (GLM). Univariate quasi-Poisson models were constructed using the log population of communes as an offset and considering overdispersion patterns. The correlations between covariables were assessed using the Spearman coefficient. Only significant variables at 95% risk were retained for further analyses.

Multivariate analyses were performed according to the methodology developed by Breiman (classification and regression tree (CART) analysis) [24] to classify the communes based on AE risk. This methodology only retains the main covariates among the collinear variables, thereby generating a tree in which the terminal nodes represent classes of communes with common characteristics. The resulting classification was analysed using a quasi-Poisson GLM to estimate standardised incidence ratios.

Case–control study of habitats at a local scale

A univariate comparison of the buffers surrounding case and control habitats was performed using the Wilcoxon test for quantitative variables and the Fisher's exact test for categorical variables. Only significant variables were retained for further analyses.

Multivariable analyses were carried out using the hierarchical ascendant classification on the multiple correspondence analysis results. We determined the most homogeneous land cover and climate groups independent of the AE status of the residents within the buffers [25], using v.test to describe how each variable influences each category. The AE incidence rates of the resulting classes were then analysed using a logistic model. The associated odds ratios were then estimated.

Statistical analysis was performed using R 3.0.2 software (R foundation for statistical computing, Vienna, Austria) with the Factominer and R-PART packages. The regression models were compared using Akaike information criterion. The test results were interpreted applying a fixed threshold at $\alpha = 0.05$.

Cartography

Spatial representation of the AE data was generated using ArcGIS 9.3 software. Simple Voronoï maps were used to enhance the clarity of the buffer categories and respect ethical concerns. The commune-level results are shown aggregated at the canton level for ethical reasons.

Results

Alveolar echinococcosis distribution at a national scale

The commune of residence was identified for 389 of the 407 cases registered by the FrancEchino network between 1982 and 2007. At a national level, the communes of case residences were found to be clustered (Moran's I index = 0.6 (Z = 26.48, $p < 0.01$)).

Marked correlations were often found between variables, especially when belonging to the same group. For example, most correlation coefficients between demographic variables were > 0.7, most correlation coefficients between altitude variables were > 0.7, and at least one correlation coefficient was > 0.5 in-between climate variables. In contrast, the land cover variables exhibited weaker intragroup correlations (< 0.5). Additionally, the demographic variables, the altitude variables and eight of the 15 climate variables displayed overdispersion.

The GLM univariate analysis of AE-affected and non-affected communes revealed a disparity for all variables except ((September + October) precipitation/July precipitation) and two land cover classes (heterogeneous agriculture and other).

Multivariable CART analysis showed that the climate variables provided the best discrimination between AE and non-AE communes (Figure 2A, Table 1). Five classes of communes were subsequently defined. Class 1, which represented 52% (n = 201) of the cases but only 3% of the French population (1,833,904 inhabitants), comprised communes with a mountain climate (i.e. Type 1 climate, as defined by Joly et al. [21]). The standardised incidence ratio was 133 (95% CI: 95–191), compared with Class 5 (reference class). Class 5 represented 84% of the French population (46,201,895 inhabitants) but only 38 (9.8%) cases. This class comprised communes characterised by climate types other than mountain or semi-continental and a mean annual temperature above 9.4 °C. The other classes exhibited intermediate climatic conditions (Figure 2).

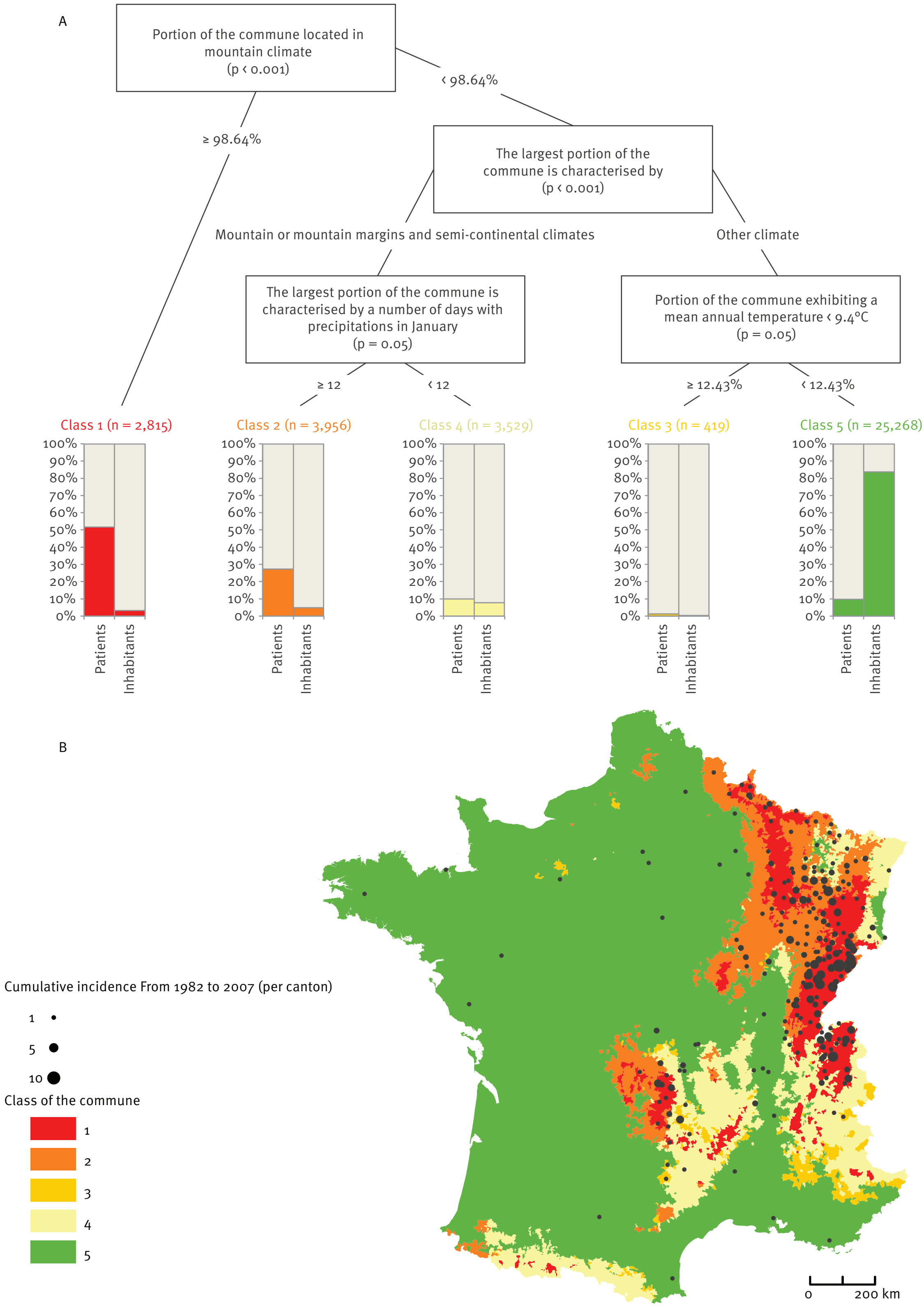
Case–control study of the respective residences in the nine most affected French départements

Of the 407 AE cases, 270 lived in the nine most affected départements. The commune of residence was identified for 266 of these cases. A precise address (i.e. hamlet or street name and number) was available for 196 of these cases. Cases with a precise address did not significantly differ from cases with non-specific addresses regarding mean age, sex ratio, clinical status or occupation (data not shown). The 74 cases without a precise address were excluded from the buffer analyses. A total of 539 control habitats were selected.

At this local scale (500 m, 1,000 m, 1,500 m and 2,000 m buffer radii as well as the communal level), the best model corresponded to a 500 m buffer radius and yielded five categories of habitat surroundings based on the Akaike information criterion (Table 2). Compared with the reference category (Category 1), only Categories 4 and 5 were associated with a significant increase in AE risk (OR: 2.40, 95% CI: 1.38–4.13 and OR: 2.72, 95% CI: 1.75–4.26, respectively) (Table 3). Category 4 consisted of habitats located in areas

FIGURE 2

National-level classification of French communes where residents are at high risk of developing alveolar echinococcosis, 1982–2007



Panel A demonstrates the commune class analysis results. The terminal nodes of the classification and regression tree (CART) analysis results correspond to the five classes of commune. The percentage of cases (left side) and inhabitants (right side) residing in each class are indicated. Class 5 is the reference class, where most of the French population is located. In contrast, most of the alveolar echinococcosis cases were located in Class 1 and Class 2 communes. Localisation of these classes and the cumulative cases during 1982 to 2007 are shown in panel B. For ethical reasons, case locations are shown at the canton level (fourth French administrative division).

Table 1

Classification of risk of alveolar echinococcosis in French communes at national level, 1982–2007

Commune class	Standardised incidence ratio[a] (95% CI)
Intercept	8.22×10^{-7} ($6.71 \times 10^{-7} - 1.83 \times 10^{-6}$)
1	133.26 (91.97–199.77)
2	48.47 (32.46–4.38)
3	28.52 (8.51–71.99)
4	11.07 (0.71–18.27)
5	1 (NA)

CI: confidence interval; NA: not applicable.

Each terminal node of the classification and regression tree (CART) analysis represented a class of French communes. Compared with Class 5, where most of the French population resides, persons residing in the communes of Classes 1, 2 and 3 were at significantly higher risk of contracting alveolar echinococcosis. The communes of Class 1 exhibit a mountain climate. The communes of Class 2 exhibit a rainy semi-continental climate, while the communes of Class 3 exhibit a non-mountainous, non-continental and cold climate.

[a] Standardised incidence ratio for each commune class displayed in Figure 2A.

with the greatest slope and elevation levels as well as a land cover dominated by broad-leaf and mixed forests. Category 5 included habitats characterised by pastures. Both Category 4 and Category 5 were also characterised by a very cold (≥25 days with cold temperature (less than −5 °C)) and humid (total annual precipitation ≥1,150 mm) mountain climate. The spatial distribution of these categories of habitat environments is shown in Figure 3.

Discussion

In this study, we identified a significant association between climatic factors and human cases of AE in France from 1982 to 2007 at national and local scales. The map indicating human AE cases and the principal climates in France clearly highlights this association (Figure 1). Nevertheless, we observed some discrepancies, such as a low incidence of AE in the southern mountainous areas of France despite the cold climate. When analysing the data at the national and local scales, we were able to include additional parameters such as rainfall effects and land cover composition. Applying this analysis, we also observed an almost-perfect fit between geographical and epidemiological data. Overall, our findings indicate that an increased risk of contracting AE in France is associated with residing in areas exhibiting the coldest winters, marked rainfall levels throughout the year and, to a lesser degree, forest and pasture land covers. Areas exhibiting a mountain climate that did not report cases of human AE, such as the southern Alps, were characterised by winters with relatively lower levels of rain and snow precipitation.

Interestingly, the distribution area of the principal hosts involved in the *E. multilocularis* life cycle in France extends far beyond the high-risk areas shown in our study. Indeed, foxes and *E. multilocularis*-permissive rodents are found in every rural area countrywide [13]. Therefore, climate does not act only by limiting the distribution of the intermediate and definitive host populations.

Our results show that AE high-risk areas are much more associated with winter temperatures and high precipitation levels than summer climatic conditions. Indeed, residing in the majority of French territories with an oceanic climate, cool summer temperatures and temperate winters was not associated with high human incidence rates of the disease. This association between AE incidence and residing in areas where winters are cold and humid corroborates previous studies conducted in China [26] and France [27]. Furthermore, several studies have highlighted a link between climatic conditions and *E. multilocularis* biomass in foxes. In Germany, foxes living in agricultural regions with high levels of precipitation harboured the greatest parasite burden [28,29]. Furthermore, the degree of fox infection was negatively associated with annual temperatures in the German federal state of Saxony-Anhalt [30]. The mechanism by which cold and humid winters enable successful completion of the parasite life cycle remains to be explained. One hypothesis demonstrated in Alaska suggests that snow acts as a parasite life cycle facilitator [31]. The overall distribution of AE observed throughout the northern hemisphere supports this hypothesis [2,32]. Regular snowy periods during the winter may greatly affect the predator–prey relationship by assisting foxes to capture rodents and thus increasing the degree of fox infection during late winter and early spring [33]. Climatic conditions may also support the conservation of *E. multilocularis* eggs in the environment. Although cold temperatures do not affect egg viability, hot and dry episodes during the summer can easily destroy the eggs [34]. Therefore, regions exhibiting cold winters, cool summers and a humid climate throughout the year may best support the *E. multilocularis* life cycle. The relatively low incidence of human AE in the southern Alps and eastern Pyrenees may be due to the relatively hot and dry summers, despite the cold winters exhibited in these regions. Additionally, these mountain regions are fragmented with deep valleys, which reduce the amount of contact between different fox populations. This may support autochthonous AE foci, as shown in northern Italy [35], or impede infected foxes from importing the parasite following the extinction of local *E. multilocularis* populations. In southern France, only the western part of the Pyrenean mountains and a few patches in the southern Alps and Massif Central exhibit climatic conditions conducive to AE transmission. In these areas, AE transmission may not be perennial because the foci are relatively small and there is limited host exchange between the foci and other permissive areas [36].

Table 2

Classification of land cover and climate in buffers of a 500 m radius around habitats in the nine départements in France most affected by alveolar echinococcosis, 1982–2007

Variable	v.test[a]
Category 1 (48 patients, 193 controls)	
Mean annual temp ≥ 9.4 and < 10.4 °C	**17.147148**
Number of days with cold temp (< −5 °C) ≥ 14 and < 25	**13.488042**
Mean elevation < 304 m	**12.684608**
Number of rainy or snowy days in January ≥ 13	9.087546
Total annual precipitation ≥ 940 and < 1,150 mm	8.942823
Total annual precipitation ≥ 800 and < 940 mm	8.914855
Range elevation < 61 m	7.851899
Number of rainy days in July ≥ 9	7.56979
Mountain margins and semi-continental climate (type 2)	6.171585
Difference between July and January mean temp. ≥ 14.7 and < 15.7 °C	6.088195
Category 2 (4 patients, 16 controls)	
Total annual precipitation ≥ 710 and < 800 mm	9.863617
Difference between July and January mean temp. ≥ 14.7 and < 15.7 °C	7.757912
Number of rainy days in July ≥ 6 and < 7	6.857535
Degraded oceanic climate (type 3)	6.857535
Altered oceanic climate	6.6954
Category 3 (45 patients, 179 controls)	
Difference between July and January mean temp. ≥ 16.9 °C	**16.971824**
Mean annual temp. ≥ 10.4 and < 11.4 °C	**14.648773**
Number of days with hot temp. (> 30 °C) ≥ 15 and < 23	**14.494255**
Number of rainy days in July ≥ 8 and < 9	**12.257087**
Number of rainy or snowy days in January ≥ 9 and < 11	6.288545
Number of days with cold temp. (< −5 °C) ≥ 14 and < 25	5.616076
Category 4 (31 patients, 52 controls)	
Range elevation ≥ 124 and < 230 m	**13.688276**
Mean slope ≥ 12.5%	**13.031426**
Range slope ≥ 29.9	**10.958377**
Range elevation ≥ 230 m	9.745691
Number of days with cold temp. (< −5 °C) ≥ 25	8.943433
Range slope ≥ 19.3 and < 29.9	8.873805
Total annual precipitation ≥ 1,150 mm	8.865216
Broad-leaf and mixed forest	8.100202
Mean slope ≥ 6.7 and < 12.5	7.5422
Mountain climate (type 1)	7.313873
Category 5 (67 patients, 99 controls)	
Mean annual temp. < 9.4 °C	**20.812435**
Number of days with cold temp. (< −5 °C) ≥ 25	**13.021636**
Difference between July and January mean temp. ≥ 15.7 and < 16.9 °C	**10.621712**
Mountain climate (type 1)	9.925993
Number of days with hot temp. (> 30 °C) < 4	9.340607
Mean elevation ≥ 740 m	9.256912
Number of days with hot temp. (> 30 °C) ≥ 4 and < 9	8.237715
Number of rainy days in July ≥ 9	7.154073
Total annual precipitation ≥ 1,150 mm	6.75911
Pastures	5.155408

Entries In bold are variables with a v.test > 10.

[a] v.test describes how the variable influences a category. It specifies how much the proportion of the modality of a variable within the category differs from the proportion in other categories. A variable modality was considered to be specific for a category when |v.test| > 3 with $p < 0.01$. For more readability, we only show the variables with the most influence producing a positive impact on the category.

Table 3

Odds ratios associated with land cover and climate classification of the 500 m-radius buffers in the nine French départements most affected by alveolar echinococcosis, 1982–2007

Category of habitat surroundings	Number of patients/ controls	Odds ratio (95% CI)
1	48/193	1 (NA)
2	4/16	1.01 (0.28–2.89)
3	45/179	1.01 (0.64–1.59)
4	31/52	2.40 (1.39–4.13)
5	67/99	2.72 (1.75–4.26)

CI: confidence interval; NA: not applicable.

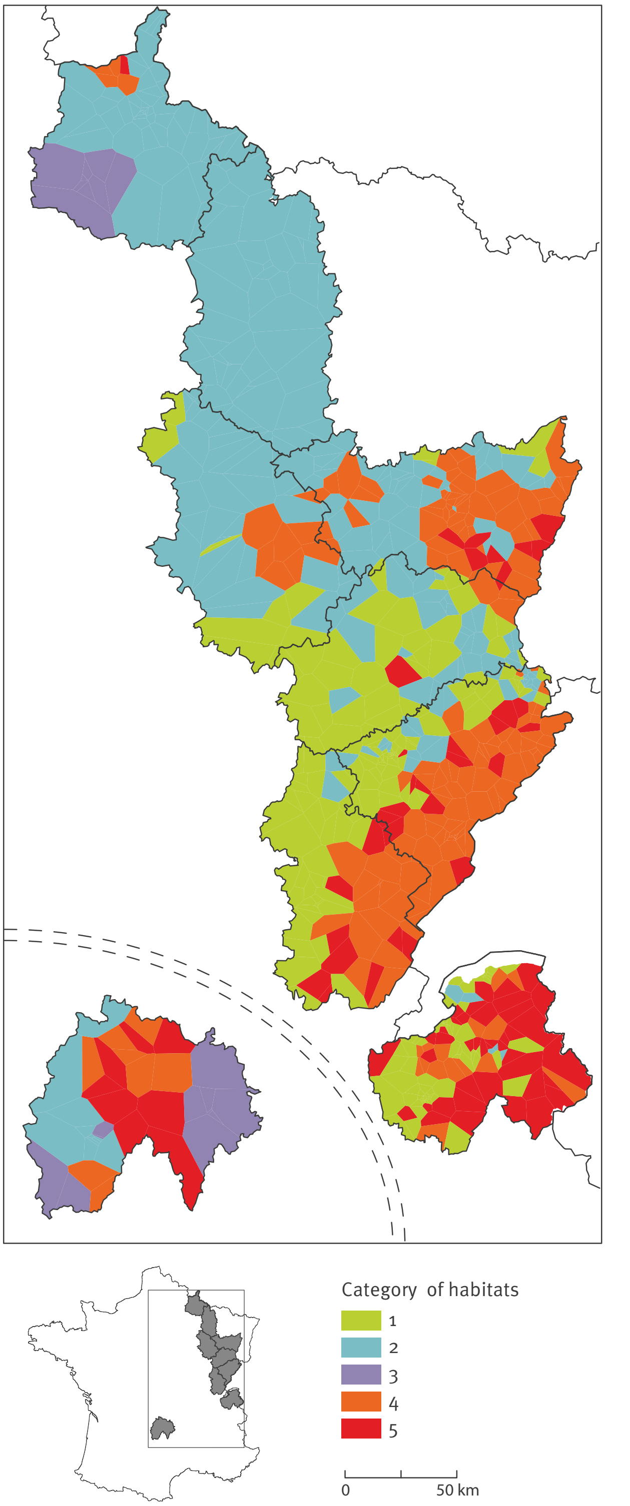
At a local scale in China, Pleydell et al. observed marked variations in AE prevalence between villages located less than 10 km apart in Zhang County, Ningxia, China, in an area spanning about 4,000 km² [16]. Moreover, human AE cases in France are irregularly dispersed, as hotspots of higher endemicity were observed at a finer scale within hyperendemic clusters [37]. Our study shows that the heterogeneous pattern of human AE incidence correlates with climate and land cover distribution at a local scale. AE incidence is also closely associated with human life habits, which change over time. Depending on the country, the most frequent individual AE risk factors include a person's sex, region of residence, agricultural or pastoral occupation, dog ownership and gardening practices [3,4,6-8]. In neighbouring Germany, the highest-risk behaviour associated with AE was farming, and gardeners were only at risk if they cultivated leaf or root vegetables [4]. These behavioural factors may partially explain the heterogeneous pattern of human AE distribution.

Our study of human AE cases complements investigations focusing on the sylvatic life cycle of the parasite [12,36-38]. From 2001 to 2005, in an area of only 900 km² of the French Ardennes, Guislain et al. observed a north/south gradient of infestation among foxes ranging from 20% to 80%, respectively [38]. In four zones in the canton of Zurich in Switzerland, approximately 1 km in radius separated by less than 15 km, the prevalence of *E. multilocularis* in foxes varied from 11.2% (95% CI: 12.7–27.2) to 60.7% (95% CI: 40.6–78.5) [39]. The populations of intermediate hosts, such as voles, fluctuate partially due to human behaviour [40] and thereby act as a metapopulation, as observed in China by Pleydell et al. [16]. This observation therefore explains the observed variability in voles' contribution to fox alimentation and subsequent variability in fox infestation [12].

We acknowledge that this study has several limitations. First, our approach addressed the risk of contracting AE among humans over an extended time

Figure 3

Map of the land cover and climate classification of the 500 m-radius buffers in the nine French départements most affected by alveolar echinococcosis, 1982–2007



Hierarchical clustering on principle components analysis determined five categories of habitats. Significant disparities were observed between the residence location of cases and controls even at this fine scale. Category 1 is the reference class (habitats where residents were least at risk of developing alveolar echinococcosis (AE).

Persons living in Category 4- and 5-type habitats were at higher risk of contracting AE compared with individuals residing in the rest of the area (see Tables 2 and 3). For ethical reasons, a Voronoï polygon map is shown instead of buffers.

period in a relatively expansive area. Due to the vast area and extended period, the human data are probably not 100% exhaustive. The process of data collection [17] was based on repeated inquiries with all health professionals potentially involved in case management, ranging from those diagnosing the disease to those delivering specific treatments. As AE incidence is low in most regions of France, the disease is irregularly recognised by physicians, which may lead to under-diagnosis. However, diagnostic imaging and serological testing has greatly improved over the last few decades [41] and persistent misdiagnosis of such a chronic and severe disease is becoming less common. Additionally, if under-diagnosed cases minimised AE incidence in some areas, it is unlikely that the subsequent bias would yield such a perfect fit between AE cases and climatic conditions.

Second, as AE exhibits a long incubation period, i.e. between five and 15 years [1], the environment of cases may have changed between the dates of infection and diagnosis. However, previous analysis revealed that way of life and lifelong residence location of the same group of cases was markedly stable [3]. In France, climate and rural landscape change gradually over the course of several human generations. Therefore, the area associated with an increased risk of disease transmission to humans likely remained rather stable during the study period and will not radically change in the near future. It should, however, be emphasised that omitted parameters, such as fox population and the behaviour of humans and foxes (e.g. increase in urban fox populations), may also play a role in disease transmission. Combes et al. [42] have reported *E. multilocularis* infection in foxes far west of documented endemic areas in France (eastern and central France), even if parasitic loads observed in foxes in western areas were low compared with that in endemic areas of eastern France [43]. Therefore, as AE epidemiology is still evolving in France and Europe, it is important to continue diligent surveillance of human and fox infestation.

The FrancEchino Network

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Conflict of interest

None declared.

Authors' contributions

MP, JG and RP conceived and designed the surveys used in this article, MP and JG conducted statistical analyses, MP, JG, BF, DAV and RP contributed to the interpretation of data and wrote the first draft, and all others authors contributed to collecting data, revised the article critically and approved the final version.

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